Cell

History Lessons from Bacteria

Microbes have been catapulted into the spotlight again by recent studies showing that uniquely modern phenomena, like jet lag and artificial sweeteners, can affect health by altering the microbiome (Suez et al., 2014; Thaiss et al., 2014). However, even as the nature of our current relationship with bacteria unfolds, DNA sequencing and proteomic approaches are giving us a fascinating glimpse into the history of human-bacterial interactions. By dusting off ancient human remains, recent work has uncovered some interesting findings about our ancestors' relationship with microbes.

Moche jar with fine line painting and figural seal on top. Moche culture, Peru, Phase III, 4th-6th century AD. Linden-Museum Stuttgart; photograph: Anatol Dreyer; Inventory-Number: 119020.

One example involves the spread of tuberculosis (TB) to the New World. *Mycobacterium tuberculosis* strains currently found in the Americas are related to those in Europe, suggesting European origins, but archeological evidence for tuberculosis in the New World prior to European contact suggests that TB was not spread through early settlers or tradesmen. Another possible route is through human migration across the Bering land bridge during the Pleistocene era, but if this were the case, the dominance of the European lineage in the Americas would present yet another unexplained puzzle. How, then, did TB manage to get to the New World? A recent study led by Johannes Krause (Bos et al., 2014), whose previous work includes genome sequencing of ancient bacteria causing leprosy and the plague (Schuenemann et al., 2013; Bos et al., 2011), sheds some light on this historical-epidemiological mystery.

The authors isolated *M. tuberculosis* DNA from 1,000 year old Peruvian human skeletons and compared the sequences to those previously identified from an 18th century Hungarian mummy (Chan et al., 2013), to modern human TB strains, and to related bacteria from a number of different animals. Surprisingly, they found that the Peruvian *M. tuberculosis* strains were not most closely related to the other human strains, as might have been expected. Instead, they clustered with bacterial strains found in seals populating the southern hemisphere. Yes, seals. Given that hunting likely afforded ample opportunity for contact between people and seals, this suggests a rather astonishing answer to how TB may have spread from Europe to the Americas: by hitching a ride across the ocean in marine mammals.

Not only has the sequencing of ancient DNA uncovered how a deadly pathogen may have colonized the New World long before Columbus did, but it's also giving us insights into ancient microbes that stuck much closer to home. The oral cavity is home to a rich community of bacteria, whose DNA can be encased and preserved within dental plaque for thousands of years. Since our ancestors didn't benefit from regular visits to the dental hygienist, this provides a source of material from which ancient oral microbiomes can be examined and has permitted work showing that with the advent of agriculture came a shift in the oral bacteria that cause gum disease (Adler et al., 2013). A study earlier this year, led by Enrico Cappellini, looks into the more recent past by sampling the dental plaque from German medieval skeletons (Warinner et al., 2014).

The study combines DNA sequencing and proteomic approaches to paint a picture of microbial pathogenicity, host immunity, and diet in the Middle Ages. Despite changes in diet and dental hygiene since that time, it seems that we share some of the same pathogenic oral bacteria with our medieval counterparts. In addition, the molecular machinery

Fossilized plaque on teeth of middle-aged man from Dalheim, Germany, ca. AD 1100. Photo credit: Christina Warinner.

allowing bacteria to mount broad, low-level resistance to antibiotics was present even back then, as were host proteins involved in the innate immune response. Remarkably, some molecular remnants of food were also preserved in the plaque. Although leafy greens don't fossilize well, the study presents paleobiological evidence that the medieval diet included broccoli-related vegetables, among other foodstuffs. Given that diet can affect microbiome composition, the accessibility of ancient dietary habits to genomic and proteomic analysis may help us better understand how changing nutrition has impacted the microbiome throughout history.

As DNA sequencing technologies continue to advance, we'll likely get an even closer look at the complex ways in which human and microbial histories have intertwined. In addition, given that proteins tend to be more stable than DNA, proteomic approaches may open a window even farther into the past than we've been able to access until now. Apart from giving us a slightly apprehensive view of our cetacean friends, or a sense of common humanity with the ancients the next time we eat some broccoli, moving forward, these kinds of studies promise to give us a more complete picture of the effects of microbes on human health, both past and present.

REFERENCES AND RECENT RELATED PAPERS

Adler, C.J., Dobney, K., Weyrich, L.S., Kaidonis, J., Walker, A.W., Haak, W., Bradshaw, C.J., Townsend, G., Sołtysiak, A., Alt, K.W., et al. (2013). Nat. Genet. *45*, 450–455, e1.

Bos, K.I., Schuenemann, V.J., Golding, G.B., Burbano, H.A., Waglechner, N., Coombes, B.K., McPhee, J.B., DeWitte, S.N., Meyer, M., Schmedes, S., et al. (2011). Nature *478*, 506–510.

Bos, K.I., Harkins, K.M., Herbig, A., Coscolla, M., Weber, N., Comas, I., Forrest, S.A., Bryant, J.M., Harris, S.R., Schuenemann, V.J., et al. (2014). Nature *514*, 494–497.

Chan, J.Z., Sergeant, M.J., Lee, O.Y., Minnikin, D.E., Besra, G.S., Pap, I., Spigelman, M., Donoghue, H.D., and Pallen, M.J. (2013). N. Engl. J. Med. *369*, 289–290.

Schuenemann, V.J., Singh, P., Mendum, T.A., Krause-Kyora, B., Jäger, G., Bos, K.I., Herbig, A., Economou, C., Benjak, A., Busso, P., et al. (2013). Science *341*, 179–183.

Suez, J., Korem, T., Zeevi, D., Zilberman-Schapira, G., Thaiss, C.A., Maza, O., Israeli, D., Zmora, N., Gilad, S., Weinberger, A., et al. (2014). Nature *514*, 181–186.

Thaiss, C.A., Zeevi, D., Levy, M., Zilberman-Schapira, G., Suez, J., Tengeler, A.C., Abramson, L., Katz, M.N., Korem, T., Zmora, N., et al. (2014). Cell *159*, 514–529.

Warinner, C., Rodrigues, J.F., Vyas, R., Trachsel, C., Shved, N., Grossmann, J., Radini, A., Hancock, Y., Tito, R.Y., Fiddyment, S., et al. (2014). Nat. Genet. *46*, 336–344.

Cindy Lu